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Cognitive training-related changes in hippocampal activity associated with recollection in older adults

Brenda A. Kirchhoff[a], **Benjamin A. Anderson**[b,1], **Staci E. Smith**[a], **Deanna M. Barch**[b,c,d], and **Larry L. Jacoby**[b]

Brenda A. Kirchhoff: kirchhoffbr@umsl.edu; Benjamin A. Anderson: andersonb@bethelu.edu; Staci E. Smith: ses5db@umsl.edu; Deanna M. Barch: dbarch@wustl.edu; Larry L. Jacoby: lljacoby@wustl.edu

[a]Department of Psychology, University of Missouri - St. Louis, St. Louis, MO 63121, USA

[b]Department of Psychology, Washington University in St. Louis, St. Louis, MO 63130, USA

[c]Department of Radiology, Washington University in St. Louis, St. Louis, MO 63130, USA

[d]Department of Psychiatry, Washington University in St. Louis, St. Louis, MO 63130, USA

Abstract

Impairments in the ability to recollect specific details of personally experienced events are one of the main cognitive changes associated with aging. Cognitive training can improve older adults' recollection. However, little is currently known regarding the neural correlates of these training-related changes in recollection. Prior research suggests that the hippocampus plays a central role in supporting recollection in young and older adults, and that age-related changes in hippocampal function may lead to age-related changes in recollection. The present study investigated whether cognitive training-related increases in older adults' recollection are associated with changes in their hippocampal activity during memory retrieval. Older adults' hippocampal activity during retrieval was examined before and after they were trained to use semantic encoding strategies to intentionally encode words. Training-related changes in recollection were positively correlated with training-related changes in activity for old words in the hippocampus bilaterally. Positive correlations were also found between training-related changes in activity in prefrontal and left lateral temporal regions associated with self-initiated semantic strategy use during encoding and training-related changes in right hippocampal activity associated with recollection during retrieval. These results suggest that cognitive training-related improvements in older adults' recollection can be supported by changes in their hippocampal activity during retrieval. They also suggest that age differences in cognitive processes engaged during encoding are a significant contributor to age differences in recollection during retrieval.

Keywords

aging; encoding strategy; fMRI; hippocampus; memory retrieval

Corresponding Author: Brenda A. Kirchhoff, Ph.D., University of Missouri - St. Louis, Department of Psychology, One University Boulevard, St. Louis, MO 63121, Phone: 314-516-4504, Fax: 314-516-5392, kirchhoffbr@umsl.edu.

[1]Present address: Division of Social Sciences, Bethel University, McKenzie, TN 38201, USA

1. Introduction[2]

The ability to accurately retrieve memories of personally experienced events is one of the cognitive skills most impaired by aging (for reviews see Balota et al., 2000; Jacoby and Rhodes, 2006; Kausler, 1994). Dual process models of memory retrieval propose that past experiences can be remembered based on cognitively-controlled retrieval of an event (recollection) or recognized based on a relatively automatic sense of familiarity in the absence of the ability to retrieve the specific details of an event (familiarity) (Jacoby and Dallas, 1981; Mandler, 1980; Yonelinas, 1994). Research comparing memory retrieval in young versus older adults has shown that aging impairs recollection while leaving familiarity relatively intact (Hay and Jacoby, 1999; Howard et al., 2006; Jacoby et al., 2001; Perfect and Dasgupta, 1997; for a review see Yonelinas, 2002).

Research on the neural correlates of memory retrieval strongly suggests that the hippocampus plays a critical role in supporting recollection. Hippocampal lesions in animals (Fortin et al., 2004; Sauvage et al., 2008) and humans (Aggleton et al., 2005; Cipolotti et al., 2006; Manns et al., 2003; Song et al., 2011; Wais et al., 2006) result in recollection impairments. In healthy young adults, positive correlations have been found between hippocampal volumes and the ability to remember the spatial locations and temporal order of studied faces (Rajah et al., 2010). Functional neuroimaging studies have also reported hippocampal activity associated with recollection during retrieval in healthy young adults. For example, the hippocampus is more active when young adults report recognizing words on the basis of recollection as compared to familiarity (Eldridge et al., 2000; Wheeler and Buckner, 2004; Yonelinas et al., 2005). Studies that have modeled recollection signals using nonlinear recognition memory confidence functions have also revealed hippocampal activity associated with recollection (Daselaar et al., 2006a, b). In addition, greater hippocampal activity has been found during correct than incorrect contextual memory retrieval (Cansino et al., 2002; Kahn et al., 2004; Ross and Slotnick, 2008).

Structural and functional neuroimaging studies suggest that age-related changes in hippocampal function may play an important role in age-related changes in recollection. Healthy aging is associated with reductions in hippocampal volume (Jernigan et al., 2001; Rajah et al., 2010; Raz et al., 2005). Structural equation modeling has suggested that these reductions in hippocampal volume may mediate the relationship between age and recollection (Yonelinas et al., 2007). During episodic memory retrieval, reduced activity in the left subiculum (a subregion of the hippocampal formation) has been found in older relative to young adults when older adults recollect fewer studied words (Cabeza et al., 2004). When recollection is modeled using a nonlinear recognition memory confidence function, reduced recollection signals have also been reported in the left hippocampus in older adults when they recollect fewer studied words (Daselaar et al., 2006b). Alterations in hippocampal recollection signals as assessed by contextual memory retrieval accuracy measures have also been found in older adults. Specifically, Kukolja et al. (2009) reported that older adults had greater activity during incorrect than correct contextual memory retrieval in a left anterior hippocampal region in which young adults had greater activity during correct than incorrect contextual memory retrieval. In contrast, Duverne et al. (2008) found that older adults had greater activity during correct than incorrect contextual memory retrieval in a left posterior hippocampal region that did not show significant differences in brain activity during correct versus incorrect contextual memory retrieval in young adults.

[2]**Abbreviations:** fMRI, functional Magnetic Resonance Imaging; BOLD, blood oxygen level-dependent; MPRAGE, magnetization prepared rapid gradient echo; ISI, interstimulus interval, ROI, region of interest

Numerous studies have shown that cognitive training can improve older adults' memory (for reviews see Lustig et al., 2009; Rebok et al., 2007; Verhaeghen et al., 1992; Zehnder et al., 2009), including their ability to recollect previously experienced events (Belleville et al., 2006; Hill et al., 1990; Jennings and Jacoby, 2003; Jennings et al., 2005; Kirchhoff et al., 2012; Yesavage et al., 1990). For example, in a study that examined the effects of semantic encoding strategy training on older adults' memory performance, self-initiated encoding strategy use, and brain activity patterns during intentional encoding, we found that they were less likely to consciously recollect intentionally encoded words than young adults prior to training (Kirchhoff et al., 2012). Teaching older adults to use pleasantness, personal relevance, and sentence generation strategies to intentionally encode words significantly improved their recollection such that it no longer differed from that of young adults' after training. Semantic strategy training also increased older adults' brain activity during encoding in prefrontal and left lateral temporal regions associated with semantic processing and self-initiated use of verbal encoding strategies (Kirchhoff and Buckner, 2006; Kirchhoff et al., 2005; Petersen et al., 1989; Poldrack et al., 1999; Vandenberghe et al., 1996).

To date, the relationship between cognitive training-related increases in recollection and brain activity during memory retrieval in older adults has not been directly explored. Thus, little is currently known regarding the role that the hippocampus may play in supporting older adults' cognitive training-related improvements in recollection. As noted above, prior lesion, structural neuroimaging, and functional neuroimaging research suggests that the hippocampus plays a central role in supporting recollection in both young and older adults. Therefore, the hippocampus may also support cognitive training-related improvements in recollection in older adults. Two recent functional magnetic resonance imaging (fMRI) studies have reported that mnemonic training can increase older adults' hippocampal activity during memory retrieval (Belleville et al., 2011; Hampstead et al., 2012), which is consistent with the prediction that cognitive training-related changes in hippocampal activity during memory retrieval in older adults are associated with improvements in recollection. However, the relationship between changes in hippocampal activity and recollection was not directly examined in these studies. Therefore, it is not clear whether cognitive training-related changes in hippocampal activity supported improvements in older adults' recollection.

This paper explores whether cognitive-training related increases in older adults' recollection are associated with changes in their hippocampal activity during memory retrieval. We investigated the relationship between training-related changes in recollection and hippocampal activity during retrieval in older adults who were trained to use pleasantness, personal relevance, and sentence generation strategies to intentionally encode words. We hypothesized that training-related changes in recollection would be positively correlated with training-related changes in hippocampal activity during retrieval, which would suggest that the hippocampus can support cognitive training-related changes in recollection in older adults. We also explored the relationship between training-related changes in brain activity associated with self-initiated semantic strategy use during encoding and training-related changes in hippocampal activity during retrieval. We hypothesized that there would be positive correlations between training-related changes in brain activity during encoding in prefrontal and left lateral temporal regions associated with older adults' self-initiated semantic encoding strategy use and training-related changes in hippocampal activity during retrieval.

2. Material and Methods

2.1 Study Design Overview

In this study older adults' brain activity during encoding and retrieval of single words, and their self-initiated encoding strategy use, were assessed before and after two days of semantic encoding strategy training (Figure 1). The effects of training on memory performance, brain activity during encoding, and self-initiated encoding strategy use have previously been reported for the participants in this study (Kirchhoff et al., 2012). This paper focuses on the relationship between the effects of training on recollection and hippocampal activity during memory retrieval.

2.2 Participants

Behavioral and functional magnetic resonance imaging (fMRI) data from fourteen older adults (mean age = 72.0, range 66 – 81; mean years of education = 14.7, SD = 2.9; 7 Females/7 Males) are presented in this paper. Informed consent was provided in accordance with Washington University's Human Studies Committee guidelines. Participants were right-handed native English-speakers, had normal or corrected-to-normal vision, reported no significant neurological or psychiatric history, and were not taking psychiatric medications or medications known to influence the blood oxygen level-dependent (BOLD) hemodynamic response. The Short-Blessed (Katzman et al., 1983) was administered to screen for dementia (all participants had < six errors; mean errors = 0.8, SD = 1.1). Participants were also screened for glaucoma, significant heart disease, untreated hypertension, diabetes, kidney disease, thyroid conditions, active cancer, previous chemotherapy treatment, and alcoholism. fMRI data during retrieval were not available for two older adults who were included in our prior paper due to technical difficulties or an inability to complete the retrieval fMRI scans due to fatigue.

2.3 Pretraining fMRI Session

2.3.1 fMRI Data Acquisition—A Siemens 3.0 Tesla Allegra scanner (Erlangen, Germany) was used to collect structural and functional magnetic resonance imaging data. An Apple Power Macintosh G4 computer (Apple, Cupertino, CA) and PsyScope software (Cohen et al., 1993) controlled the stimulus display and recorded responses from a magnet-compatible fiber-optic keypress device interfaced with a PsyScope button box. Stimuli were displayed on a screen at the head of the magnet bore with an LCD projector and were viewed using a mirror attached to the head coil. Headphones dampened scanner noise and head movement was minimized using padding and tape. High-resolution structural images (1 × 1 × 1.2 mm) were acquired using a sagittal T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence (TR = 2.3 s, TE = 2.83 ms, flip angle = 9°, TI = 900 ms). Functional images were acquired using $T2^*$-weighted asymmetric spin-echo echo-planar sequences sensitive to BOLD contrast. Four functional scans of 96 whole-brain images (32 4 × 4 × 4 mm contiguous axial slices acquired parallel to the AC-PC plane, TR = 2.5s, TE = 25 ms, flip angle = 90°) were collected per participant during encoding. Six functional scans of 88 whole-brain images (32 4 × 4 × 4 mm contiguous axial slices acquired parallel to the AC-PC plane, TR = 3.0s, TE = 25 ms, flip angle = 90°) were collected per participant during retrieval. The first four images in each scan were discarded to allow T1 magnetization to stabilize.

2.3.2 Stimuli—Stimuli for the fMRI sessions were four to seven letter English words, which were presented centrally in uppercase letters. Word lists were counterbalanced across tasks and scanning sessions. They were also matched for word frequency, length, and syllable count. Each word list consisted of half abstract (e.g., love, hope) and half concrete (e.g., table, flower) words.

2.3.3 Encoding—During the first two scans of the pretraining fMRI session, older adults performed an intentional encoding task in which they were instructed to carefully study each presented word in anticipation of a later, unspecified memory test. They were also instructed to make a right-handed keypress whenever a word appeared to ensure that they were attending to the presented words. Older adults performed an abstract/concrete incidental encoding task during the third and fourth scans of the pretraining fMRI session. They decided whether each word represented an abstract or a concrete entity, and made a right-handed keypress to indicate their decision for each word. During all encoding scans, three blocks of fixation plus signs (30 s) alternated with two blocks of words (70 s, 20 words per block) so that a total of 80 words were presented during each encoding task. Ten additional seconds of fixation were acquired at the beginning of every scan to allow T1 magnetization to stabilize. During word trials, a word was presented for 3250 ms and was followed by a fixation plus sign presented for 250 ms.

2.3.4 Retrieval—Immediately following the last encoding scan, older adults' memory for the words studied during intentional encoding was assessed using Remember/Know/New recognition memory decisions (Tulving, 1985) during three fMRI scans (fMRI and behavioral data from three subsequent abstract/concrete task retrieval scans are not presented here). The retrieval scans consisted of a total of 80 old word, 80 new word, and 80 fixation plus sign trials presented in pseudorandom order so that every trial type was equally likely to be preceded and followed by every other trial type (Buckner et al., 1998). Four additional fixation plus sign trials were presented at the beginning and end of each scan. A plus sign was presented for 3000 ms during fixation trials. Individual words were presented for 2775 ms, and were followed by fixation plus signs presented for 225 ms, during old and new word trials. Participants were instructed to make a Remember response if they recognized that a word had been encountered during the encoding scans and were able to consciously recollect aspects of its prior presentation. They were instructed to make a Know response if they recognized that a word had been encountered during the encoding scans but could not consciously recollect aspects of its prior occurrence. In addition, they were instructed to make a New response if they thought they had not seen the word during the encoding scans. Although the relationship is imperfect, Remember responses are a measure of conscious recollection while Know responses are a measure of a feeling of familiarity in the absence of recollection (Yonelinas, 2002; Yonelinas and Jacoby, 1995). Participants' responses were recorded using a magnet-compatible fiber-optic keypress device. They used their left index finger to make a Remember response, their right index finger to make a Know response, and their right middle finger to make a New response.

2.3.5 Self-Initiated Encoding Strategy Questionnaire—Immediately after leaving the MRI scanner, older adults completed a self-initiated encoding strategy questionnaire. They rated how often they used twenty-four possible encoding strategies during the intentional encoding scans, including the pleasantness ("Thought about whether each word was pleasant or unpleasant"), personal relevance ("Thought about the personal relevance of each word"), and sentence generation ("Constructed phrases, sentences, and/or stories that contained one studied word") strategies that they were trained to use in this study, and how often they used no encoding strategy ("Read each word but did not use any particular strategy to try to remember the words"). They rated the frequency of their use of these strategies using a scale of never, rarely, sometimes, usually, or always. These ratings were converted into numerical values for statistical analyses (1 = never, 2 = rarely, 3 = sometimes, 4 = usually, and 5 = always).

2.4 Semantic Encoding Strategy Training

2.4.1 Strategies Trained—Older adults completed two semantic encoding strategy training sessions on separate days after the pretraining neuroimaging session. During the first strategy training session, participants were taught to use pleasantness, personal relevance, and sentence generation strategies to intentionally encode lists of words. Specifically, they were taught to decide whether each presented word was pleasant or unpleasant and to think about why they felt that way (pleasantness strategy), to think about how each word was personally relevant to them (personal relevance strategy), and to form a sentence that contained each presented word (sentence generation strategy). After participants were given extensive practice using each of these semantic encoding strategies, they were instructed to study additional word lists using whichever semantic encoding strategy, or combination of semantic encoding strategies, they felt worked best for them. During the second session, they practiced using each of the semantic encoding strategies on multiple word lists and then were again allowed to choose whichever semantic encoding strategy or strategies they wanted to use to study additional word lists. We allowed older adults to choose which semantic encoding strategy or strategies to practice at the end of the cognitive training sessions instead of training them to use just one semantic encoding strategy throughout training because we thought they would be most likely to initiate self-selected strategies during the posttraining fMRI session.

2.4.2 Stimuli—Stimuli for these training sessions were four to seven letter English words, which were presented centrally in uppercase letters. Word lists were matched for word frequency, length, and syllable count, and consisted of half abstract and half concrete words.

2.4.3 Encoding Word Lists—Older adults practiced using semantic encoding strategies on several lists of words during the strategy training sessions. Each word on these encoding word lists was presented for 3225 ms, and was followed by a 225 ms blank screen interstimulus interval (ISI). Difficulty was gradually increased throughout training by increasing the number of words on these lists (first list: 18, last list: 144).

2.4.4 Retrieval Word Lists and Performance Feedback—Immediately following each encoding word list, older adults were shown a retrieval word list. Half of the words on these lists were words that had just been studied during the encoding list that preceded it, and half were new (old/new status was counterbalanced across participants). Participants made a Remember/Know/New decision for each word, and indicated the outcome of their decisions by making keypresses on a computer keyboard. Each word was presented for up to 2775 ms, and was followed by a 225 ms blank screen ISI. Immediately after a response was made, or the response window was exhausted, older adults were given visual feedback for 1500 ms on the accuracy of their response ("Correct": Remember or Know response to an old word or a New response to a new word, "Miss": New response to an old word, "False Alarm": Remember or Know response to a new word, or "Please respond faster": no response to a word). They also received feedback on their performance at the end of every recognition word list. An accuracy summary screen appeared, which informed each older adult of the percentage of the time he/she was correct when he/she made Remember, Know, and New responses, what percentage of the time he/she did not make a response to a word on time, and what percentage of the time he/she made a correct response for the word list overall. Difficulty was gradually increased throughout training by increasing the number of words shown during these retrieval word lists (first list: 36, last list: 288).

2.5 Posttraining fMRI Session

Older adults completed the posttraining fMRI scanning session the day after the second strategy training session. The posttraining scanning session occurred approximately two weeks after the pretraining scanning session (range 8 – 18 days). Both scanning sessions used identical structural and functional scanning parameters and encoding and retrieval task designs. Participants were not explicitly told to use the strategies that they learned in the training sessions during the posttraining fMRI session.

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2.6 Behavioral Analyses

The effects of training on overall recognition memory performance, Remember Hits (Remember responses to old words), Know Hits (Know responses to old words), Misses (New responses to old words), and reaction times for keypress responses during retrieval were examined using paired sample *t*-tests. Overall recognition memory performance was measured by subtracting the proportion of Remember and Know False Alarms (Remember and Know responses to new words) from the proportion of Remember and Know Hits.

2.7 fMRI Data Analyses

fMRI data preprocessing included adjustment for slice timing differences using ideal sinc interpolation, correction for odd-even slice intensity differences, mode normalization, and motion-correction using a rigid-body rotation and translation correction. fMRI data were resliced into 3 mm isotropic voxels and transformed into the stereotaxic atlas space of Talairach and Tournoux (1988) using a template constructed from 16 young and 16 older adult T1-weighted MPRAGE scans acquired on the MRI scanner used in this study (Snyder et al., 2002). The general linear model implemented in an in-house analysis and display package was used to analyze functional data (Miezin et al., 2000). Brain activity during retrieval trials was modeled as an extended gamma function (Boynton et al., 1996) and scaled to percent signal change. Run mean and slope were coded as effects of no interest. *Z*-transformed reaction times for responses to old words were included as covariates to control for training-related changes in reaction times. Data were smoothed using a two-voxel isotropic Gaussian filter.

2.8 Hypothesis-Driven Analyses of the Relationship Between Training-Related Changes in Recollection and Hippocampal Activity During Memory Retrieval

The relationship between older adults' training-related changes in recollection and hippocampal activity during memory retrieval was first examined by conducting Pearson Product Moment correlation analyses between training-related changes (posttraining minus pretraining) in the proportion of Remember Hits and training-related changes in activity for all 80 old words studied during intentional encoding in each voxel of a bilateral hippocampal anatomical mask derived from prior work (Wang et al., 2008). Resulting r statistics were converted to z statistics and plotted over the combined young/old anatomical image. The activation map was corrected for multiple comparisons using a combined p value/cluster size threshold of $p < 0.025/26$ voxels, which corresponded to a two-tailed false positive rate of $p < 0.05$ for the whole anatomical mask. This threshold/cluster-size requirement provides protection against type I error (Forman et al., 1995, McAvoy et al., 2001) and was chosen based on Monte-Carlo simulations via AlphaSim (Ward, 2000). Activity during all 80 old word trials was used as the measure of hippocampal activity in fMRI analyses so that training-related changes in the number trials used to estimate hippocampal activity would not confound analyses of the relationships between training-related changes in hippocampal activity and memory performance.

Voxel-based Pearson Product Moment correlation analyses between training-related changes in the proportion of Know Hits and activity for all 80 old words studied during intentional encoding were also conducted within the hypothesis-driven hippocampal anatomical region of interest (ROI) described above using the same p value/cluster size threshold. The goal of this analysis was to examine whether training-related changes in hippocampal activity during retrieval were selectively associated with training-related changes in recollection, or whether they were also driven by training-related changes in familiarity.

2.9 Exploratory Analysis of the Relationship Between Training-Related Changes in Recollection and Brain Activity During Memory Retrieval

To further examine the relationship between training-related changes in recollection and hippocampal activity, and to investigate whether training-related changes in recollection were associated with training-related changes in activity in regions beyond the hippocampus, a whole-brain exploratory analysis of the relationship between older adults' training-related changes in recollection and brain activity during retrieval was conducted. In this analysis, Pearson Product Moment correlations were calculated between training-related changes in the proportion of Remember Hits and brain activity in response to old words in each voxel of the brain. Resulting r statistics were converted to z statistics and plotted over the combined young/old anatomical image. The statistical significance threshold for the functional activation map was set to $p < 0.01$ with a minimum voxel size of 5 voxels, uncorrected for multiple comparisons. An automated algorithm identified activation peaks in the functional activation map. ROIs were then created that included all continuous voxels within 12 mm of an activation peak, inclusively masked by the functional activation map.

2.10 Analyses of the Relationship Between Training-Related Changes in Prefrontal and Left Lateral Temporal Activity Associated with Semantic Strategy Use During Encoding and Hippocampal Activity During Retrieval

In our prior paper from this dataset that examined the effects of semantic strategy training on older adults' brain activity during encoding (Kirchhoff et al. 2012), we identified several prefrontal and left lateral temporal regions previously associated with semantic processing and/or self-initiated verbal encoding strategy use that had strong positive correlations between training-related changes in activity and older adults' memory performance. This suggests that these regions support self-initiated semantic encoding strategy use in older adults. However, we did not find strong correlations between training-related changes in self-initiated use of the trained semantic encoding strategies and training-related changes in brain activity in these regions, most likely because participants were allowed to practice whichever encoding strategy or strategies they felt worked best for them at the end of the training sessions. Therefore, to explore whether semantic encoding strategy training altered older adults' hippocampal activity during retrieval by increasing their self-initiated use of semantic strategies during encoding, we examined the relationship between training-related changes in brain activity during encoding in the prefrontal and left lateral temporal regions associated with older adults' self-initiated semantic encoding strategy use (medial superior frontal (BA 6), left middle frontal/precentral (BA 6), left dorsal posterior inferior frontal (6/44/9), left ventral posterior inferior frontal (BA 44), left anterior inferior frontal (BA 45), and left middle/superior temporal (BA 21/22)) and training-related changes in brain activity during retrieval in hippocampal ROIs identified from our hypothesis-driven and exploratory analyses using Pearson Product Moment correlation analyses ($p < 0.05$, one-tailed).

3. Results

3.1 Semantic Encoding Strategy Training Improved Older Adults' Ability to Recollect Intentionally Encoded Words

Memory retrieval accuracy data for the fourteen older adults in this study who had analyzable brain activity data during retrieval are presented in Table 1 (see Supplementary Table 1 for reaction time data). Training improved older adults' recognition memory overall ($t(13) = 5.53$, $p < 0.001$, $d = 1.00$). It also increased their Remember Hits ($t(13) = 4.43$, $p < 0.01$, $d = 1.15$), and decreased their Know Hits ($t(13) = −2.63$, $p < 0.05$, $d = −0.68$) and Misses ($t(13) = −2.31$, $p < 0.05$, $d = −0.66$) (Table 1). Taken together, these results suggest that semantic encoding strategy training selectively improved recollection of intentionally encoded words in the older adults whose hippocampal activity during retrieval is analyzed in this paper. This result is consistent with the memory retrieval findings in the larger older adult cohort in our prior paper (Kirchhoff et al., 2012).

3.2 Training-Related Changes in Recollection Were Positively Correlated with Training-Related Changes in Hippocampal Activity During Memory Retrieval

Analysis of the relationship between older adults' training-related changes in recollection and hippocampal activity during retrieval in the hypothesis-driven anatomical ROI revealed a positive correlation between training-related changes in Remember Hits and activity for old words in the left hippocampus (−38, −2, −11; Figure 2). Inspection of the scatterplot from this analysis reveals that older adults with the largest training-related increases in recollection had training-related increases in their activity during retrieval. However, due to the substantial variability in the degree to which older adults benefited from training in this study, training did not significantly change mean brain activity ($t(13) = -0.05$, $p > 0.1$, $d = 0.00$) in this region. There were no clusters within either hippocampus with a significant negative correlation between training-related changes in Remember Hits and activity for old words.

The relationship between training-related changes in recollection and activity for old words during retrieval throughout the brain was also examined using a whole-brain exploratory correlation analysis. Training-related changes in Remember Hits and activity for old words were positively correlated in the both the left (−22, −21, −13) and right (27, −20, −15) hippocampus (Table 2, Figure 3), further suggesting that the hippocampus supported training-related improvements in recollection in this study. However, training did not significantly alter mean brain activity in these regions overall (left: (13) $t = 0.13$, $p > 0.1$, $d = 0.04$; right: $t(13) = -2.04$, $p < 0.07$, $d = -0.72$), consistent with the results of the hypothesis-driven anatomical ROI analysis. Training-related changes in Remember Hits and brain activity for old words were also positively correlated within several additional brain regions, including regions within prefrontal cortex (Table 2). There were no significant negative correlations between training-related changes in Remember Hits and brain activity for old words.

3.3 Training-Related Changes in Hippocampal Activity During Memory Retrieval Were Selectively Associated with Training-Related Changes in Recollection

To explore the specificity of the correlations between training-related changes in Remember Hits and hippocampal activity, we explored the relationships between training-related changes in Know Hits and activity for old words in the hippocampus. First, we conducted a voxel-based Pearson Product Moment correlation analyses within the hypothesis-driven hippocampal anatomical ROI, but did not find any significant correlations between training-related changes in Know Hits and activity for old words. We also examined correlations between training-related changes in Know Hits and activity for old words in the left hippocampal ROI identified in the hypothesis-driven Remember Hits analysis (Figure 2), and the left and right hippocampal regions identified in the whole-brain exploratory Remember Hits analysis (Figure 3). Training-related changes in Know Hits and brain activity were not significantly correlated in the left hypothesis-driven ($r = -.29$, $p > 0.1$) or exploratory ($r = -.30$, $p > 0.1$) ROIs, but there was a trend toward a negative correlation in the right hypothesis-driven ROI ($r = -.48$, $p < 0.09$). Taken together, the pattern of correlations between training-related changes in Remember and Know Hits and hippocampal activity for old words suggests that training-related increases in hippocampal activity reflected increases in recollection but not familiarity.

3.4 Training-Related Changes in Right Hippocampal Activity During Memory Retrieval Were Positively Correlated with Training-Related Changes in Prefrontal and Left Lateral Temporal Activity During Encoding

Training-related changes in activity in prefrontal and left lateral temporal regions that support older adults' self-initiated semantic strategy use during encoding were not significantly correlated with training-related changes in activity in the left hippocampal region during retrieval identified in the hypothesis-driven anatomical ROI analysis (Table 3). However, there was a trend toward a significant correlation between training-related changes in activity in the left middle frontal/precentral gyrus (BA 6) and training-related changes in activity in the left exploratory hippocampal ROI. Importantly, training-related changes in activity during encoding in all of the regions associated with self-initiated semantic encoding strategy use were significantly positively correlated with training-related changes in activity in the right exploratory hippocampal ROI except for the left anterior inferior frontal region (BA 45), which had a trend toward a significant positive correlation. These results suggest that training-related changes in self-initiated semantic encoding strategy use contributed to training-related changes in hippocampal activity associated with recollection during memory retrieval.

4. Discussion

This paper explored the effects of a semantic encoding strategy training protocol that enhances older adults' recollection on their hippocampal activity patterns during memory retrieval. Training-related changes in Remember Hits were positively correlated with training-related changes in activity for old words in the hippocampus bilaterally. Positive correlations were also found between training-related changes in activity in prefrontal and left lateral temporal regions associated with self-initiated semantic strategy use during encoding and training-related changes in right hippocampal activity associated with recollection during retrieval. The implications of these results are discussed below.

While training-related changes in hippocampal activity during retrieval were positively correlated with training-related changes in Remember Hits, they were not significantly correlated with training-related changes in Know Hits. This suggests that training-related changes in hippocampal activity associated with training-related changes in Remember Hits were not due to differences in scanner signal across scanning sessions, task practice effects, etc., but instead reflected hippocampal support of training-related improvements in recollection. The lack of significant correlations between training-related changes in Know Hits and hippocampal activity further suggest that training-related changes in hippocampal activity were driven by training-related changes in recollection and not familiarity.

The positive correlations between training-related changes in Remember Hits and activity for old words in the left and right hippocampus in this study are consistent with prior research suggesting that the hippocampus plays a central role in supporting recollection in both young and older adults (Aggleton et al., 2005; Cabeza et al., 2004; Cansino et al., 2002; Daselaar et al., 2006b; Dulas and Duarte, 2011; Duverne et al., 2008; Eldridge et al., 2000; Rajah et al., 2010; Yonelinas et al., 2007). It is also consistent with recent studies that demonstrated that cognitive training can increase hippocampal activity during memory retrieval (Belleville et al., 2011; Hampstead et al., 2012). Importantly, this study extends prior research by beginning to shed light on the relationships between training-related changes in cognitive processing and hippocampal activity and the mechanisms of age-related changes in recollection.

The positive correlations between training-related changes in Remember Hits and hippocampal activity during retrieval suggest that even though hippocampal volume is reduced in older adults (Jernigan et al., 2001; Rajah et al., 2010, Raz et al., 2005), the hippocampus can still support cognitive training-related improvements in their recollection. Interestingly, the significant correlations between training-related changes in prefrontal and left lateral temporal activity during encoding and right hippocampal activity during retrieval suggest that age differences in cognitive processes engaged during encoding are a significant contributor to age differences in recollection. These age differences in the cognitive processes engaged during encoding may reflect age-related alterations in prefrontal structure and function (for reviews see Gunning-Dixon et al., 2009; Raz and Rodrigue, 2006). Importantly, the prefrontal and left lateral temporal regions whose activity we found to be correlated with hippocampal activity during retrieval are regions associated with self-initiated semantic strategy use during encoding (Kirchhoff et al. 2012). Therefore, it is likely that the changes in hippocampal activity in this study resulted from training increasing older adults' use of semantic strategies during encoding (and hence increasing activity in these prefrontal and lateral temporal regions), instead of training improving the function of the hippocampus per se. Semantic encoding strategy training may improve older adults' recollection by facilitating their ability to form distinctive memory traces during encoding that contain detailed information about the studied words (e.g., what encoding strategy they used to learn the word). During retrieval, these elaborate memory traces could enhance older adults' ability to reinstate contextual information from encoding (e.g., what encoding strategy(ies) they used) to constrain retrieval and facilitate recollection (i.e., source constrained retrieval, Jacoby et al. 2005b; Shimizu and Jacoby, 2005). Prior research has suggested that impairments in source constrained retrieval play an important role in age-related changes in recollection (Jacoby et al., 2005a; Velanova et al., 2007). Multiple prefrontal regions demonstrated positive correlations between training-related changes in activity for old words during memory retrieval and training-related changes in recollection in this study, which is consistent with the possibility that training enhanced older adults' source constrained retrieval.

An important question for future research is whether cognitive training can improve older adults' hippocampal function by inducing beneficial changes in its structure and/or improving its processing efficiency. A recent study demonstrating that aerobic exercise training can increase older adults' hippocampal volumes, and that these volumetric increases are associated with improvements in spatial memory, suggests that experiences that enhance older adults' memory can improve older adults' hippocampal function (Erickson et al., 2011).

A limitation of this study is that training did not significantly increase older adults' mean activity in hippocampal regions associated with recollection. This is likely due to the substantial variability in older adults' training-related changes in recollection. Although this variability may have prevented us from finding significant training-related changes in mean hippocampal activity, it did allow us to find positive correlations between training-related changes in recollection and hippocampal activity. Another limitation of this study is that it did not include a no treatment control group of older adults who were scanned twice. Therefore, we cannot completely rule out the possibility that some of the changes that we observed in hippocampal activity between the pre- and posttraining fMRI scans are due to task practice effects. However, the positive correlations between training-related changes in activity in prefrontal and left lateral temporal regions associated with self-initiated semantic strategy use during encoding and training-related changes in right hippocampal activity associated with recollection during retrieval suggest that semantic encoding strategy training was an important contributor to changes in recollection and hippocampal activity during retrieval. Interestingly, hippocampal activity tended to decrease following cognitive training in older adults who did not have a substantial improvement in recollection from training. Understanding what drives these decreases in hippocampal activity in older adults who do not benefit from semantic encoding strategy training is an important topic for future research. In older adults with relatively large increases in recollection following training, hippocampal activity tended to increase after training, particularly within the left hippocampus. The results of this study suggest that these increases in hippocampal activity are driven by increases in hippocampal dependent recollection.

5. Conclusions

In conclusion, the results of the data analyses conducted in this paper suggest that the hippocampus can support cognitive training-related improvements in older adults' recollection. They also suggest that age differences in cognitive processing during encoding may play an important role in age differences in recollection and hippocampal activity during retrieval. Furthermore, this study demonstrates that training-related changes in older adults' cognitive processing during encoding can contribute to training-related changes in recollection and hippocampal activity during retrieval. Therefore, cognitive training protocols that target age differences in cognitive processing during encoding, such as age differences in self-initiated encoding strategy use, may be an effective approach for reducing older adults' impairments in recollection and age-related changes in hippocampal activity during memory retrieval.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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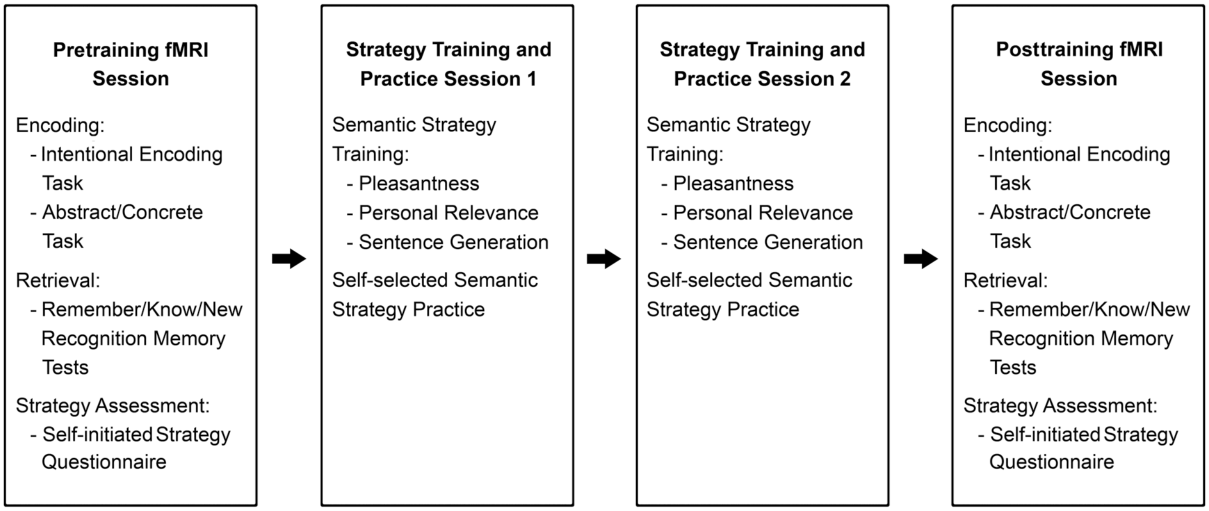

Figure 1.

Study design. During the pre- and posttraining fMRI sessions, older adults' brain activity was measured during encoding (intentional encoding and abstract/concrete tasks) and retrieval (Remember/Know/New task) of single words. Immediately after leaving the MRI scanner, their self-initiated encoding strategy use during intentional encoding was assessed using a strategy questionnaire. Older adults were taught to use three semantic encoding strategies to intentionally encode words (pleasantness, personal relevance, and sentence generation) during two strategy training sessions. They were given extensive practice using each of these strategies individually. In addition, they were given the opportunity to practice using whichever semantic encoding strategy, or combination of semantic encoding strategies, they felt worked best for them at the end of each strategy training session. Adapted from Kirchhoff et al. (2012) with permission from Oxford University Press.

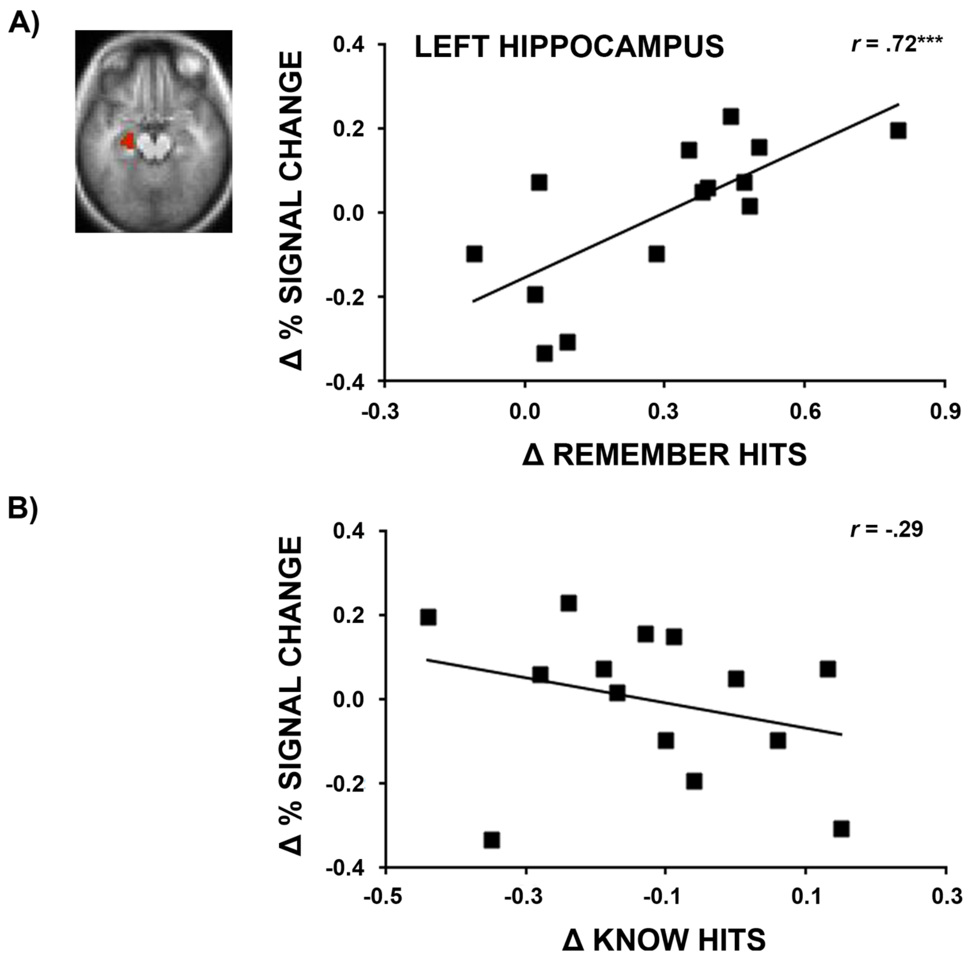

Figure 2.

Training-related changes in recollection and brain activity during memory retrieval were selectively positively correlated in a left hippocampal region identified in a hypothesis-driven anatomical ROI analysis. A) Training-related changes in recollection (as assessed by Remember Hits) and brain activity for old words were positively correlated in the left hippocampus ($p < 0.05$, corrected). B) In contrast, there was not a significant correlation between training-related changes in Know Hits and activity in this region. ***$p < 0.01$.

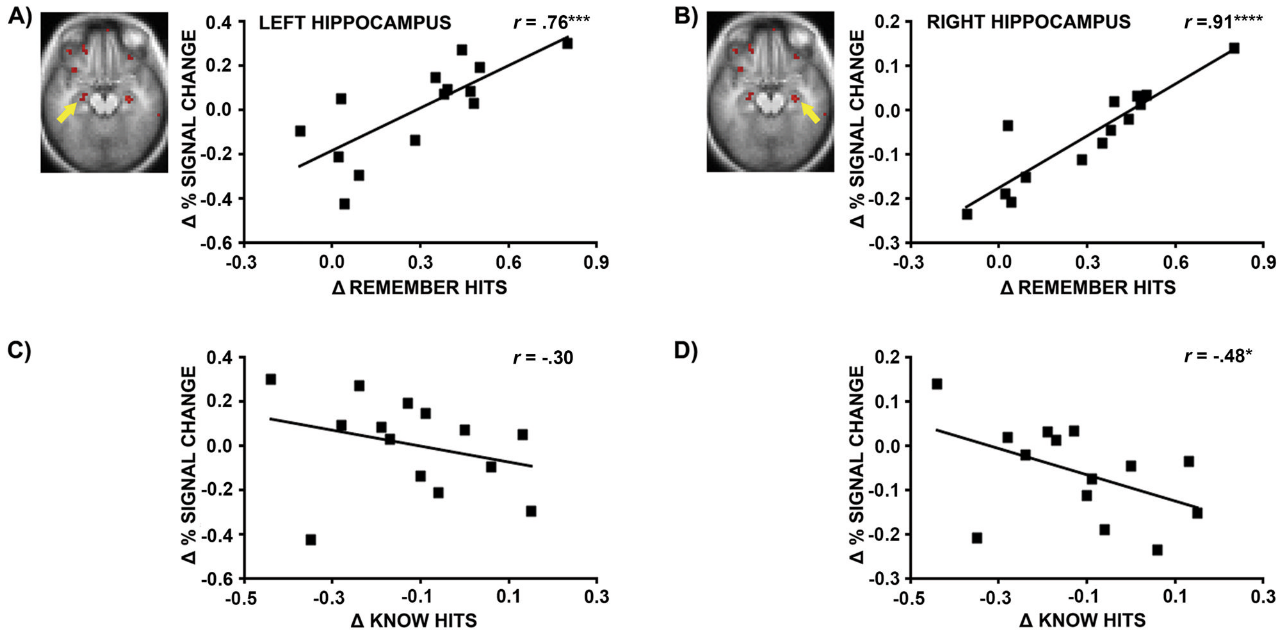

Figure 3.
A whole-brain exploratory analysis revealed selective positive correlations between training-related changes in recollection and brain activity during memory retrieval in the hippocampus bilaterally. Significant positive correlations between training-related changes in recollection (as assessed by Remember Hits) and brain activity for old words were found in the A) left and B) right hippocampus in a whole-brain exploratory correlation analysis ($p < 0.01$, uncorrected). However, training-related changes in Know Hits and brain activity for old words were not significantly correlated in either the C) left or D) right hippocampal regions. *$p < 0.1$, ***$p < 0.01$, ****$p < 0.001$.

Table 1

Overall recognition memory, Remember Hits, Know Hits, and Misses for older adults before and after semantic encoding strategy training.

	Recognition Memory	Remember Hits	Know Hits	Misses
Pretraining	.29 (.15)	.32 (.21)	.27 (.15)	.36 (.19)
Posttraining	.49 (.24)****	.61 (.29)***	.15 (.20)**	.23 (.23)**

Note. Means and standard deviations (in parentheses) for overall recognition memory, Remember Hits, Know Hits, and Misses. Asterisks indicate a significant training effect (

** $p < 0.05$,

*** $p < 0.01$,

**** $p < 0.001$).

Table 2

Regions with significant positive correlations between training-related changes in recollection and brain activity for old words during memory retrieval identified from a whole-brain exploratory analysis.

Region	BA	x y z (mm)	*z*	Voxels
L Hippocampus	-----	−22 −21 −13	2.97	10
R Hippocampus	-----	27 −20 −15	3.87	7
L Sup Frontal	8	−10 33 51	3.15	12
L Mid Frontal	46	−32 46 19	2.81	7
R Mid Frontal	46	32 39 21	2.85	6
R Mid/Inf Frontal	46	35 41 5	2.88	10
L Inf Frontal	47	−35 15 −13	3.48	10
R Inf Frontal	47	29 27 −13	3.24	10
R Precentral/Insula	6	37 1 15	3.10	16
Ant Cingulate	24/33	−1 22 19	3.04	21
Post Cingulate	31	0 −30 40	2.81	11
R Sup Temporal	41	34 −28 16	3.41	13
R Lingual	17	13 −89 4	2.82	8
L Cerebellum	-----	−45 −47 −39	2.72	9

Note. BA = Brodmann’s area; x y z (mm) = location of activation peak in Talairach coordinates;

z = z score of peak voxel

Table 3

Correlations between training-related changes in brain activity in prefrontal and left lateral temporal regions that support older adults' self-initiated semantic strategy use during encoding and training-related changes in brain activity in hippocampal regions associated with recollection during memory retrieval.

Region	Hypothesis-Driven Left Hippocampal ROI	Exploratory Left Hippocampal ROI	Exploratory Right Hippocampal ROI
Medial BA 6	.31	.30	.54**
Left BA 6	.33	.37*	.49**
Left BA 6/44/9	.32	.34	.52**
Left BA 44	.29	.28	.57**
Left BA 45	.27	.27	.46*
Left BA 21/22	.24	.24	.55**

Note. ROI = Region of Interest;

* $p < 0.1$,

** $p < 0.05$.